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(71)(72) Applicant and Inventor: BOLS, Mikael [DK/DK]; Solbakken 3B4, DK-8240 Risskov (DK).

(74) Agent: PLOUGMANN, VINGTOFT & PARTNERS; Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).

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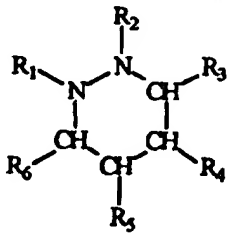
(54) Title: HYDROXYHEXAHYDROPYRIDAZINES

(57) Abstract

The present invention relates to hydroxyhexahydropyridazines of general formula (I). These compounds are found to be inhibitors of glycoside cleaving enzymes and it is therefore envisaged that such compound may be used for treatment of or for controlling diabetes, cancer, or AIDS caused by human immunodeficiency virus. Furthermore, such compounds may be used in plant protection. The mechanism for the action of the compound is that they, in protonated form, resemble the transition state of natural substrates for the glucosidases in question.



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HYDROXYHEXAHYDROPYRIDAZINES

FIELD OF THE INVENTION

The invention relates to a new group of chemical compounds, hydroxyhexahydropyridazines (formula I herein), and their biological application and use. It has been found that the compounds according to the invention inhibit glycoside cleaving enzymes such as glycosidases and glycosyl phosphorylases. The invention also relates to such compounds for use as a medicament, e.g. in the treatment of the diseases: diabetes, cancer and AIDS, as well as the use of these compounds in crop protection.

BACKGROUND OF THE INVENTION

In the group of enzymes that convert carbohydrates, some of the most important are those which hydrolyse or phosphorylate glycosidic linkages to mono- and oligosaccharides or saccharide phosphates, respectively. These enzymes, which are called glycosidases or glycoside phosphorylases, are important for all growth and development of living organisms. They participate in a wide range of important biological events such as digestion of carbohydrate-foodstuffs, glycoprotein modification in eukariotes, and degradation of polysaccharides and glycoconjugates.

Chemical compounds that inhibit glycoside-cleaving enzymes can be used to block certain biochemical processes, and consequently such compounds may be applied for treatment of diseases and crop protection.

Diabetes may, e.g., be treated by controlling or reducing the addition of glucose to the blood. This can either be done by inhibition of the α-glucosidase catalysed degradation of foodstuff-carbohydrates to glucose or by inhibition of the glycogen phosphorylase catalysed degradation of the carbohydrate storage.

Cellulose cannot be degraded to glucose by humans, but can on the other hand be degraded by micro-organisms, fungi and insects (crop pests), living of plant material. Cellulase and β-

glucosidase inhibitors may, thus, block the crop pests metabolism in a for humans harmless way, and thus be applied for crop protection.

In recent years, the interest for development and synthesis of inhibitors of glycosidases have grown tremendously. The most effective glycosidase inhibitors are polyhydroxylated piperidines such as nojirimycin and isofagomine, 5-amino-5-deoxy-gluconolactam, polyhydroxylated pyrrolidines, the indolizidine alkaloids swainsonin and castanospermin, the polyhydroxylated aminocyclopentanes and the polyhydroxylated aminocyclohexene acarbose.

As mentioned above, inhibitors of α-glucosidases can be used for treatment of diabetes. The strongest known α-glucosidase inhibitors are acarbose and castanospermin. Acarbose is used as a pharmaceutical for treatment of diabetes, but its effect is limited, and it has side effects. There is thus a need for alternative α-glucosidase inhibitors.

As mentioned above, diabetes may alternatively be treated with a glycogen phosphorylase inhibitor. A known strong glycogen phosphorylase inhibitor is isofagomine (WO 95/24391). Isofagomine is however difficult to prepare. There is thus a need for more readily available strong glycogen phosphorylase inhibitors.

Also as mentioned above, inhibitors of β-glucosidase may be used for crop protection and the strongest known β-glucosidase inhibitor is isofagomine (Jespersen et al. *Angew. Chem.Int. Ed.* 33 (1994) 1778-9.). Isofagomine is however difficult to prepare and thus unsuitable for crop protection. There is thus a need for more readily available strong β-glucosidase inhibitors.

Furthermore, inhibitors of α-mannosidase, α- and β-fucosidase and α-glucosidase can potentially be used in the treatment of AIDS. There is thus a need for new strong α-mannosidase, α- and β-fucosidase and α-glucosidase inhibitors.

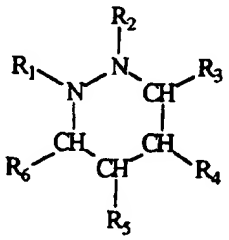
Furthermore, the inhibitors of β-glucuronidase and other glycosidases can potentially be applied to reducing cancer metastases. There is thus a need for new strong glycosidase inhibitors.

Thus, the aim of the present invention is to provide novel glycosidase inhibitors. The inventor has surprisingly found that compound of the hydroxyhexahydropyridazine type possess glycosidase inhibitor properties as well glycogen phosphorylase inhibitor properties.

Some other hydroxyhexahydropyridazines are known in the literature. Paulsen and Steinert (*Chem. Ber.* **1970** *103* 1834-45) made 3-methyl-di- and trihydroxyhexahydropyridazines more specifically (3R, 4S, 5R, 6S)-6-methyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4S, 5R, 6S)-6-methyl-3,4,5-trihydroxy-1,2-diazinane, (3R, 4S, 5R, 6S)-1,6-dimethyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4S, 5R, 6S)-1,6-dimethyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4R, 5R)-3-methyl-4,5-dihydroxy-1,2-diazinane, (3S, 4R, 5R)-1-acetyl-3-methyl-4,5-dihydroxy-1,2-diazinane and (3S, 4R, 5R)-1-acetyl-4,5-diacetoxy-3-methyl-1,2-diazinane. These compounds have a stereochemistry unlike naturally occurring sugars. Various monohydroxy-hexahydropyridazine-3-carboxylic acids (specifically 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-hydroxy-1,2-diazinane and 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-acetoxy-1,2-diazinane) and derivatives have been described (1) *J. Chem. Soc. Perkin. Trans. 1* **1976** *22* 2390-4. 2) *J. Chem. Soc. D.* **1969** *18* 1079-80. 3) *Heterocycles* **1977** *7* 119-22. 4) *Experientia* **1970** *26* 122-3. 5) *J. Chem. Soc. C* **1971** *3* 522-6. 6) *J. Chem. Soc. Chem. Commun.* **1994** 1867-8.). No biological activity was described in connection with any of these compounds.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to novel compounds of the general formula I



wherein

R_1 designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, optionally substituted C_{1-7}-alkylcarbonyl, optionally substituted C_{1-7}-alkoxycarbonyl, optionally substituted aryl(C_{1-7}-alkoxy)carbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl,

di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy or $-CH_2-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; or R_1 designates two C_{1-7}-alkyl groups thereby leading to a quaternarisation of the nitrogen atom to which R_1 (the two C_{1-7}-alkyl groups) is/are attached; and

R_2 designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy or $-CH_2-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide;

each of R_3, R_4, R_5, and R_6 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, amino, optionally substituted C_{1-7}-alkylamino, di(optionally substituted C_{1-7}-alkyl)amino, tri(optionally substituted C_{1-7}-alkyl)ammonium, carboxy, carboxyamino, optionally substituted C_{1-7}-alkylcarbonylamino, optionally substituted arylcarbonylamino, nitro, sulphanyl, C_{1-7}-alkylthio, cyano, azido, optionally substituted C_{2-7}-alkenyl, optionally substituted C_{2-7}-alkynyl, optionally substituted aryl, optionally substituted C_{1-7}-alkylcarbonyl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide;

or a salt thereof;

with the provisos that

(a) at least one of R_3, R_4, R_5 or R_6 designates optionally substituted C_{1-7}-alkyl, carboxy, cyano, optionally substituted C_{2-7}-alkenyl, optionally substituted C_{2-7}-alkynyl, optionally substituted aryl, optionally substituted C_{1-7}-alkylcarbonyl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, or $-CH_2-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; and

(b) at least one of R_3, R_4, R_5 or R_6 designates hydroxy, optionally substituted C_{1-7}-alkoxy, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or -O-X, where X designates a glycosyl group of a mono-, di- or trisaccharide; and

(c) when R_3 designate (3S)-carboxy and R_4 and R_6 designate hydrogen, then R_5 designates a group different from (5S)-hydroxy; and

(d) that said compound is not selected from 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-hydroxy-1,2-diazinane, 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-acetoxy-1,2-diazinane, (3R, 4S, 5R, 6S)-6-methyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4S, 5R, 6S)-6-methyl-3,4,5-trihydroxy-1,2-diazinane, (3R, 4S, 5R, 6S)-1,6-dimethyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4S, 5R, 6S)-1,6-dimethyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4R, 5R)-3-methyl-4,5-dihydroxy-1,2-diazinane, (3S, 4R, 5R)-1-acetyl-3-methyl-4,5-dihydroxy-1,2-diazinane, (3S, 4R, 5R)-1-acetyl-4,5-diacetoxy-3-methyl-1,2-diazinane.

The compounds according to the invention have glucosidase inhibitor activity and may, thus, be used for the treatment of and for controlling diabetes, AIDS, and cancer as well as for crop protection. These compounds are, as described below, easier to prepare than most known inhibitors of glycoside cleaving enzymes.

DETAILED DESCRIPTION OF THE INVENTION

Glycoside-cleaving enzymes work by catalysing the cleavage of the glycosidic linkage in a glycoside to a unstable high energy intermediate, a transition state, by stabilising this in its catalytic pocket (see Fig. 1). The transition state is a carbocation, which is in resonance equilibrium with an oxocarbenium ion. Chemical compounds that electronically and sterically resemble transition state to a high extent, transition state analogues, are expected to bind strongly to the enzyme's catalytic pocket and thereby prevent, i.e. inhibit, its action. The compounds according to the present invention, hydroxyhexahydropyridazines, as per formula I, e.g. compound **1**, are basic and will be protonated under neutral conditions. Thereby two forms of the protonated hydrazine are formed (see Fig 1). These are in equilibria and will each represent a transitionstate-analogues of respectively the carbocation and the oxocarbenium ion of glycoside-cleavage. Hydroxyhexahydropyridazines, as **1** and derivatives, are therefore

potentially strong inhibitors of glycoside-cleaving enzymes e.g. glycosidases and glycoside phosphorylases.

In the present context, the term "C_{1-7}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 7 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, cyclopropyl, cyclopropylmethyl, butyl, *tert*-butyl, iso-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, heptyl. Preferred examples of "C_{1-7}-alkyl" are methyl, ethyl, propyl, iso-propyl, butyl, *tert*-butyl, iso-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, in particular methyl, ethyl, propyl, iso-propyl, *tert*-butyl, iso-butyl and cyclohexyl.

The term "alkoxy" is intended to mean alkyl-oxy.

Similarly, the term "C_{2-7}-alkenyl", is intended to mean a linear, cyclic or branched hydrocarbon group having 2 to 7 carbon atoms and comprising one unsaturated bond. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, and heptenyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

Similarly, the term "C_{2-7}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 7 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecanyl.

In connection with the terms "alkyl", "alkoxy", "alkenyl", and "alkynyl", the term "optionally substituted" is intended to mean that the alkyl group, the alkoxy group, the alkenyl group, or the alkynyl group, respectively, in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy, C_{1-7}-alkoxy, carboxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkylcarbonyl, formyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, amino, mono- and di(C_{1-7}-alkyl)amino; carbamoyl, mono- and di(C_{1-7}-alkyl)aminocarbonyl, amino-C_{1-7}-alkyl-aminocarbonyl, mono- and di(C_{1-7}-alkyl)-amino-C_{1-7}-alkyl-aminocarbonyl, C_{1-7}-alkylcarbonylamino, guanidino, carbamido, C_{1-7}-alkyl-carbonyloxy, sulphono, nitro, sulphanyl, C_{1-7}-alkylthio, trihalogenalkyl, halogen such as fluoro, chloro, bromo or iodo. Preferably, the substituents are selected from hydroxy, C_{1-7}-alkoxy, carboxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkylcarbonyl, formyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, amino, mono- and di(C_{1-7}-

alkyl)amino, carbamoyl, mono- and di(C_{1-7}-alkyl)aminocarbonyl, amino-C_{1-7}-alkyl-aminocarbonyl, mono- and di(C_{1-7}-alkyl)amino-C_{1-7}-alkyl-aminocarbonyl, C_{1-7}-alkylcarbonylamino, guanidino, carbamido, trihalogenalkyl, halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl may be substituted with methyl, nitro or halogen. Especially preferred examples of substituents are hydroxy, C_{1-7}-alkoxy, carboxy, optionally substituted aryl, amino, mono- and di(C_{1-7}-alkyl)amino, mono- and di(C_{1-7}-alkyl)amino, and halogen such as fluoro, chloro, bromo or iodo.

In the present context the term "aryl" is intended to mean an aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example. Furthermore, "aryl" is also intended to mean such groups where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen, sulphur, and/or oxygen atoms. Examples of such further groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, piperidinyl, coumaryl, furyl, quinolyl, indolyl, benzopyrazolyl, phenoxazonyl, among which pyridinyl, benzopyrazolyl, and imidazolyl are preferred examples.

In the present context, i.e. in connection with the term "aryl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times, with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-7}-alkoxy, carboxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-7}-alkyl)amino; carbamoyl, mono- and di(C_{1-7}-alkyl)aminocarbonyl, amino-C_{1-7}-alkyl-aminocarbonyl, mono- and di(C_{1-7}-alkyl)amino-C_{1-7}-alkyl-aminocarbonyl, C_{1-7}-alkylcarbonylamino, guanidino, carbamido, C_{1-7}-alkanoyloxy, sulphono, C_{1-7}-alkylsulphonyloxy, nitro, sulphanyl, trihalogenalkyl, halogen such as fluoro, chloro, bromo or iodo. Preferred examples are hydroxy, C_{1-7}-alkoxy, carboxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkylcarbonyl, aryl, amino, mono- and di(C_{1-7}-alkyl)amino, aryl and halogen such as fluoro, chloro, bromo or iodo.

In the present context, the term glycosyl group (of a mono-, di- or trisaccharide) is intended to mean a hexopyranosyl group, a (O-hexopyranosyl)-hexopyranosyl group or a ((O-hexopyranosyl)-O-hexopyranosyl)-hexopyranosyl group. The individual hexopyranose groups are typically

selected from glucose, mannose, galactose, fucose, glucosamine, galactosamine, N-acetyl-glucosamine, N-acetylgalactosamine, and rhamnose.

In preferred compounds of the general formula I, R_1 designates hydrogen, optionally substituted C_{1-7}-alkyl, optionally substituted C_{1-7}-alkylcarbonyl, aryl(C_{1-7}-alkoxy)carbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)-aminocarbonyl, or optionally substituted C_{1-7}-alkylcarbonyloxy; or R_1 designates two C_{1-7}-alkyl groups; and R_2 designates hydrogen or optionally substituted C_{1-7}-alkyl. More preferably, each of R_1 and R_2 independently designates hydrogen or optionally substituted C_{1-7}-alkyl, and in particular each of R_1 and R_2 independently designates hydrogen or C_{1-7}-alkyl.

With respect to the further substituents, preferred compounds are those where each of R_3, R_4, R_5, and R_6 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, amino, optionally substituted C_{1-7}-alkylamino, di(optionally substituted C_{1-7}-alkyl)amino, tri(optionally substituted C_{1-7}-alkyl)ammonium, carboxy, carboxyamino, optionally substituted C_{1-7}-alkylcarbonylamino, optionally substituted arylcarbonylamino, sulphanyl, C_{1-7}-alkylthio, cyano, azido, optionally substituted aryl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)-aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide. More preferred are those where and each of R_3 and R_6 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, carboxy, cyano, azido, optionally substituted aryl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; and each of R_4 and R_5 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, amino, optionally substituted C_{1-7}-alkylamino, di(optionally substituted C_{1-7}-alkyl)amino, carboxy, carboxyamino, optionally substituted C_{1-7}-alkylcarbonylamino, optionally substituted arylcarbonylamino, sulphanyl, C_{1-7}-alkylthio, cyano, azido, optionally substituted aryl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide. Particularly preferred are those where

each of R_3 and R_6 independently designates hydrogen, hydroxy, C_{1-7}-alkyl, carboxy, cyano, azido, C_{1-7}-alkoxycarbonyl, aminocarbonyl, C_{1-7}-alkylaminocarbonyl, or di(C_{1-7}-alkyl)amino-carbonyl; and each of R_4 and R_5 independently designates hydrogen, hydroxy, C_{1-7}-alkyl, amino, C_{1-7}-alkylamino, di(C_{1-7}-alkyl)amino, carboxy, carboxyamino, C_{1-7}-alkylcarbonylamino, cyano, azido, optionally substituted aryl, C_{1-7}-alkoxycarbonyl, aminocarbonyl, C_{1-7}-alkylamino-carbonyl, di(C_{1-7}-alkyl)aminocarbonyl, or C_{1-7}-alkylcarbonyloxy.

Furthermore, the invention covers salts of the compounds according to the invention. The preparation of pharmaceutical salts of the compounds according to the invention is well known to a professional in the field, and will not be described in detail. Examples of salt, which furthermore are pharmaceutically acceptable, includes, but is not limited to, organic carboxylic acids such as acetic acid, lactic acid, tartaric acid, maleic acid, isothionic acid, lactobionic acid, and succinic acid; organic sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid and toluene sulfonic acid, and inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfaminic acid. Also included are pharmaceutical acceptable salts of basic salts of the compounds, made with a suitable base such as alkalimetal (e.g. sodium, potassium), earth alkalimetal (e.g. magnesium), ammonium, and NW_nH_m bases where n and m are from 0 to 4, and n+m are 4, and where W is a C_{1-18}-alkyl group.

Preferred specific compound are:

4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine such as

(*4S,5R,6R*)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,

(*4R,5S,6S*)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,

(*4R,5S,6R*)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,

(*4S,5R,6S*)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,

(*4R,5R,6R*)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine, and

(*4S,5S,6S*)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,

4,5-dihydroxy-6-methyl-hexahydropyridazine such as

(*4S,5R,6S*)-4,5-dihydroxy-6-methyl-hexahydropyridazine,

(*4R,5S,6R*)-4,5-dihydroxy-6-methyl-hexahydropyridazine,

(*4R,5S,6S*)-4,5-dihydroxy-6-methyl-hexahydropyridazine, and

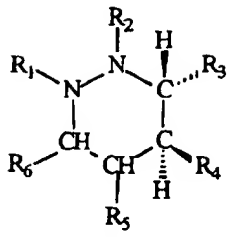
(*4S,5R,6R*)-4,5-dihydroxy-6-methyl-hexahydropyridazine,

4,5-dihydroxy-6-fluoromethyl-hexahydropyridazine,
4-fluoro-5-hydroxy-6-hydroxymethyl-hexahydropyridazine,
1-N-(2-hydroxyethyl)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,
2-N-(2-hydroxyethyl)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,
4,5-dihydroxy-hexahydropyridazine-6-carboxylic acid,
and salt of these compounds.

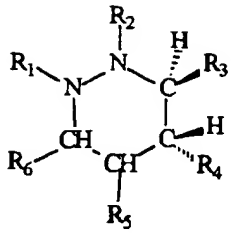
The compounds according to the invention are expected to resemble the transitionstate of natural substrates so much that they will inhibit glycoside cleaving enzymes.

It is, thus, believed that the most interesting compounds are those which mimic the stereochemisty of glucose, mannose, galactose, glucosamine, galactosamine, rhamnose or fucose because such compounds will better fit into the active site of a glycosidase. Furthermore the substituents R_3-R_6 of the compound I will then have a spatial position similar to the hydroxy groups of the natural substrate saccharide, and, thus, the substituents are more likely to fit into the corresponding pockets of the glucosidase in question. Also, if one or more of the substituents are hydroxy groups, or, alternatively, derivatives thereof, such substituents may participate in hydrogen bonding similar to the hydroxy groups of the natural substrate. This will increase the binding and thereby the inhibition, and is also likely to increase the specificity of the compound.

Thus, a preferred embodiment of the present invention relates to compounds I having any of the general formulae II, III, IV or V



II



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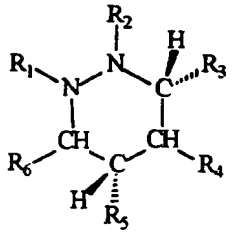
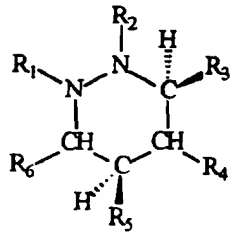


IV



V

In compounds I where the substituents R_3 and R_4, or R_3 and R_5, respectively, are substituents different from hydrogen, Formula II represents compounds that have a stereochemistry resembling D-glucose, D-mannose and D-glucosamine; Formula III represents compounds that have a stereochemistry resembling L-rhamnose; Formula IV represents compounds that have a stereochemistry resembling D-glucose, D-mannose, D-galactose, D-galactosamine and D-glucosamine; Formula V represents compounds that have a stereochemistry resembling L-fucose.

Interesting examples are compound which fulfils the criteria set forth in both of Formulae II and IV, thus having, at least partially, a stereochemistry resembling D-glucose, D-glucosamine, or D-mannose.

The present invention is also related to a pharmaceutical formulation comprising a compound I for the treatment of or for controlling diabetes, cancer or AIDS caused by human immunodeficiency virus which consist of at least one compound of the invention as described above, mixtures hereof and/or pharmaceutical salts hereof; and a pharmaceutical acceptable carrier material. Such formulations are made after the established pharmaceutical procedures, e.g. as described in *Remington's Pharmaceutical Sciences*, 17. edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). More generally, the present invention relates

to a compound I as a medicament, e.g. for the treatment of or for controlling diseases such as diabetes or cancer, or for fighting or controlling human immunodeficiency virus.

Furthermore, the invention covers a method for protecting a crop characterised by treatment of the crop with one or more compounds of the invention in an amount necessary to protect the crop.

Still further, the invention covers a method for inhibiting cellulase activity characterised by treatment of one or more compounds of the invention in an amount necessary to inhibit cellulase activity.

The invention is also intended to cover the known compound 4,5-dihydroxy-tetrahydropyridazine (formula I where $R_1 = R_2 = R_3 = R_6 = H$ and $R_4 = R_5 = OH$) as inhibitor of glycoside cleaving enzymes for treatment of diabetes, cancer, AIDS and for crop protection.

SYNTHESIS

The novel compounds of the invention can be made by the synthesis described in the reaction scheme in Fig. 2. The synthetic method includes a sequence of steps known to a professional in the field; thus, the synthetic method includes one or more of the following steps:

1) Diels-Alder reaction between a diene and a azadienophile

This reaction is as generally described in Forrest, A. K.; Schmidt, R. R.; Huttner, G.; Jibril, I. De novo Synthesis of Carbohydrates. Part 14. Preparation of 4-Amino-lyxose Derivatives. X-ray Molecular Structure of Ethyl 6-Ethoxycarbonylamino-8-hydroxymethyl-3,3-dimethyl-2,4-dioxa-7-azabicyclo(3.3.0)octane-7-carboxylate. J. Chem. Soc. Perkin. Trans. 1 1984 1981-7. or in Batchelor, M. J.; Mellor, J. M. The Use of Dichloromaleic and Bromomaleic Anhydrides in the Synthesis of Lactones by the Intramolecular Diels-Alder Reaction. J. Chem. Soc. Perkin. Trans. 1 1989 985-95. The diene can be any known 1,3-butadiene optionally substituted in the 1, 2, 3 and/or 4 position with any available substituent. Such substituents may correspond to the substituents in the compound I, or may be substituents which may be converted to a substituent in the compound I. E.g., when a R_3 substituent is present in compound I, such a substituent is normally introduced via the 1-position of the diene; analogously, when R_4, R_5

and/or R_6 substituent are present in the compound I, those substituents may directly be introduced via the 2, 3 and/or 4-position of the diene, respectively. However, the substituents R_4 and R_5 may also conveniently be introduced in a separate step, see below. Furthermore, all the substituents of the diene can normally be modified at a later stage. The diene may, e.g., be butadiene, 2,3-dimethylbutadiene, phenylbutadiene, Danishefskis diene, hexadienes, pentadiene, pentadienol, pentadienoic acid, methyl pentadienoate, ethyl pentadienoate or sorbyl alcohol. As explained such dienes may carry suitable substituents. The azadienophile is typically either 4-phenyl-1,2,4-triazol-3,5-dione or a dialkyl azodicarboxylate. The Diels-Alder reaction is carried out by mixing the diene and the dienophile in an organic solvent, e.g. selected from ethyl acetate, ethanol, methanol, dichloromethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile, dimethyl sulphoxide or dimethyl formamide. The reaction is carried out at a temperature between -50 and 200°C depending on the reactivity of the reagents, typically at a temperature between 0 and 50°C, such as around 25°C.

2) Addition to the double bond of the Diels-Alder adduct.

This reaction step can be used to introduce the substituents R_4 and/or R_5 when such substituents are absent in the diene, or when such substituents are present in the diene to reduce the partially unsaturated ring (the Diels-Alder adduct) to a fully saturated ring by the addition of hydrogen atoms (hydrogenation). The following illustrative examples of reaction conditions may be used, of course depending on the nature of the substituents R_4 and R_5.

a) Addition of hydrogen to the double bond, typically when R_4 and R_5 designate hydrogen, can be carried out by reaction of the Diels-Alder adduct with hydrogen, as generally described in J. March Advanced Organic Chemistry, 3. ed. p. 745-758, at a pressure of 1 to 100 atmospheres, typically 1-3 atmospheres, in the presence of a metal catalyst such as palladium, rhodium, Raney nickel or platinum, typically palladium, in a suitable organic solvent such as ethyl acetate, ethanol, methanol, dioxane, tetrahydrofuran, toluene or benzene.

b) Dihydroxylation of the double bond (R_4 and R_5 designate hydroxy or a derivative thereof) can be carried out with osmium tetroxide with or without N-methyl-N-morpholine as co-oxidant, as generally described in J. March Advanced Organic Chemistry, 3. ed. pp. 732-734, at 0-60°C, typically at around 25°C, for 1h to 7 days, typically ½-1 day, in a suitable solvent such

as ethyl acetate, ethanol, methanol, dichloromethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile, dimethyl sulphoxide, water or dimethyl formamide. Alternatively dihydroxylation can be carried out by epoxidation followed by acidic hydrolysis. This is done by first reaction of the Diels-Alder adduct with an oxidant, as generally described in J. March Advanced Organic Chemistry, 3. ed. pp. 735-737, such as 3-chloroperbenzoic acid or a dialkyldioxirane, typically trifluoromethylmethyl dioxirane, in a solvent such as ethyl acetate, ethanol, methanol, dichloromethane, dichloroethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile, dimethyl sulphoxide or dimethyl formamide, at 0-150°C, typically at around 25°C, for 1h to 7 days, typically ½-1 day, to give an epoxide. Secondly the epoxide is reacted with aqueous acid, as generally described in J. March Advanced Organic Chemistry, 3. ed. p. 332, e.g. aqueous perchloric acid 0.1-5% at 25-100°C for 1-100 h, typically around 5 h. The resulting hydroxy groups may subsequently or intermittently be converted to a derivative thereof, e.g. by acetylation or alkylation or glycosidation (step 5), thereby leading to other variants of the substituents R_4 and R_5.

c) Monohydroxylation can be made by hydroboration/oxidation, as generally described in J. March Advanced Organic Chemistry, 3. ed. pp. 702-707, 550. It is carried out by reaction of the Diels-Alder adduct with borane or a alkyl- or dialkylborane in an aprotic organic solvent, typically tetrahydrofuran or dioxane, at -78-100°C for 1-24 hours; then the product is oxidised with a suitable oxidant such as hydrogen peroxide. As above, the resulting hydroxy group may be converted to a derivative thereof.

d) Halogen is added (as R_4 and/or R_5), as generally described in J. March Advanced Organic Chemistry, 3. ed. pp. 724-726, by treatment of the Diels-Alder adduct with halogen such as bromine, chlorine or iodine in an inert solvent typically dichloromethane for 1-18 hours at 25-100°C.

e) Halogen and hydroxy groups (one or R_4 and R_5 is halogen and the other is hydroxy or a derivative thereof) are added by treatment, as generally described in J. March Advanced Organic Chemistry, 3. ed. pp. 726-728, with halogen in water. This is carried out by treatment of the Diels-Alder adduct with halogen in water for 1-18 hours at 25-100°C. As above, the resulting hydroxy group may be converted to a derivative thereof.

f) A hydroxy group and another substituent (one of R_4 and R_5 is halogen, alkylthio, cyano, hydrogen, optionally substituted alkyl, amino, thio, optionally substituted alkoxy or optionally substituted alkylamino and the other is hydroxy or a derivative thereof) may be introduced by first reaction of the Diels-Alder adduct with an oxidant, as generally described above. Secondly the epoxide is reacted with a nucleophile, as generally described in J. March Advanced Organic Chemistry, 3. ed. pp. 255-446. The nucleophile may, e.g., be a halide, cyanide, a sulphide, a xanthogenate, an amine, a carbanion, an alkyl group form a organometalic reagent, azide and hydride. With a halide nucleophile a halogen substituent is obtained; with a cyanide nucleophile a cyano substituent is obtained; with a sulphide nucleophile an alkylthio substituent is obtained; with a xanthogenate nucleophile a thiol substituent is obtained after treatment with sodium methoxide in methanol; with an amine nucleophile an amino, alkylamino or dialkylamino substituent is obtained; with a carbanion nucleophile an optionally substituted alkyl substituent is obtained.; with an organometallic reagent an alkyl substituent is obtained; with an azide nucleophile an azido substituent is obtained; and, finally, with a hydride nucleophile, from e.g. lithium aluminium hydride, a hydrogen "substituent" is obtained. As a reagent, the pure nucleophile, the metal, typically potassium, salt of the nucleophile, the corresponding acid form, H-Nucleophile, of the nucleophile or the trimethylsilyl derivative of the nucleophile (Me_3Si-Nucleophile) may be used. The solvent is typically ethyl acetate, ethanol, methanol, dichloromethane, dichloroethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile, dimethyl sulphoxide or dimethyl formamide. The reaction temperature is often between 25-180°C, typically 25-60°C. In some cases a Lewis acid catalysts such as borontrifluoride, tin tetrachloride or trimethylsilyl triflate is added.

3) Hydrazinolysis of phenylurazole or hydrolysis of dialkyl azodicarboxylates.

Hydrazinolysis of a phenylurazole is, e.g., carried out by mixing the compound with hydrazine-hydrate at 25-100°C for 1h to 2 days without a solvent. Hydrolysis of dialkyl azodicarboxylates is typically carried out by treatment of the dialkyl azodicarboxylate with aqueous acid such as aqueous perchloric acid 0.1-5% at 25-100°C for 1-100 h. In some cases the product will be the final compound, i.e. the introduction of any substituents R_4 and R_5 has been performed and R_1 and R_2 designate hydrogen. Alternatively, the product is subjected to the reaction steps 4) and/or 5) below, and optionally also to reaction step 2) above.

4) Substitution on nitrogen followed by separation of the products.

This step is used when R_1 and/or R_2 substituents are desired. Reaction with an alkyl halide will give a N-alkyl substituent, while reaction with an acid chloride will result in an acyl substituent. Other reactive nitrogen atoms (other substituents) are optionally protected by using protection-/deprotection schemes known to the person skilled in the art.

a) The hydrazine derivative (the adduct from step 3) is dissolved in a suitable solvent such as ethyl acetate, ethanol, methanol, dichloromethane, dichloroethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile, dimethyl sulphoxide or dimethyl formamide, and treated with an alkyl halide, which can be any commercially available alkyl halide, e.g. but not limited to methyl iodide, ethyl iodide, 2-bromoethanol, benzyl bromide, allyl bromide or propyl bromide, in excess. The reaction is carried out at 0-200°C typically at 25°C for 0.1 hour to 7 days depending on whether both of R_1 and R_2 should be alkylated or not. The reaction is stopped and the product is separated. In some cases the product will be the final compound, in some cases the product is subjected to reactions described under 4b) and/or 5) below and/or 2) above.

b) The hydrazine derivative (optionally treated as described under 4b) is dissolved in a suitable solvent such as ethyl acetate, ethanol, methanol, dichloromethane, dichloroethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile, dimethyl sulphoxide or dimethyl formamide, and treated with an acylhalide or anhydride, which can be any commercially available acyl halide or anhydride, e.g.,. but not limited to acetic anhydride, benzoyl chloride, pivaloyl chloride, propanoyl chloride, butanoyl chloride or crotonyl chloride, in excess. The reaction is carried out at 0-200°C typically at 25°C for 0.1 hour to 7 days. The reaction is stopped and the product is separated. In some cases the product will be the desired compound I, and in some cases the product is further subjected to reaction step 5) below or reaction step 2) above.

5) Glycosidation of hydroxy groups.

The compound is typically reacted with a the trichloroacetimidate of a sugar as generally described in Schmidt, R. R. Angew.Chem. 1986, 98, 213-236. The compound is dissolved in a

suitable solvent such as ethyl acetate, dichloromethane, dichloroethane, chloroform, toluene, dioxane, tetrahydrofuran, benzene, acetone, acetonitrile or dimethyl formamide, and a perbenzyl glycosyl trichloroacetimidate, such as tetra-O-benzyl glucosyl trichloroacetimidate, tetra-O-benzyl mannosyl trichloroacetimidate, tetra-O-benzyl galactosyl trichloroacetimidate, tetra-O-benzyl fucosyl trichloroacetimidate or tetra-O-benzyl rhamnosyl trichloroacetimidate, is added together with a Lewis acid catalyst, such as borontrifluoride, tin tetrachloride or trimethylsilyl triflate, and the mixture is reacted at -78 to 25°C for 0.1 to 24 hours. After this reaction the benzyl groups are removed by dissolving the product in ethyl acetate adding palladium on carbon and reacting with hydrogen at 1 to 50 atmospheres at 25°C for 1 to 24 hours. The product will typically be the final compound.

For therapeutic use in a method to treat or control diabetes, cancer or human immuno-deficiency virus can one of the compounds in this invention or its salt be given in the form of a pharmaceutical formulation consisting of at least one compound of the invention, and/or pharmaceutical salts hereof; and a pharmaceutical acceptable carrier material. Suitable carriers are known to a professional and can vary with form and the method used for treatment in the pharmaceutical formulation.

EXAMPLES

The following examples illustrate the invention further, and how, e.g., 1 can be made from commercially available materials (see Fig. 3) and penta-2,4-dien-1-ol (2), which can be made as described in *J. Chem. Soc.* 1990, p 1640., and *tert*-butylhypochlorite, prepared as described by M. J. Mintz et al. *Organic Synthesis* Coll. Vol 5, John Wiley & sons New York 1973, ed. H. E. Baumgarten, p 184-7.

Example 1

(6R/6S)-2,4-dioxo-6-hydroxymethyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclonon-7-ene (4). 4-Phenylurazol (3, 20 g, 113 mmol) were dissolved in EtOAc (60 ml) at 0°C and *tert*-butylhypochlorite (12.4 g) was added, where after a red, homogeneous solution was obtained. After 5 min. penta-2,4-dien-1-ol (2, 10.0 g, 119 mmol) was added, and the solution was stirred while being heated over 30 minutes to room temperature. After filtration and concentration,

chloroform (200 ml) was added to the residue, and the mixture was filtered again. The filtrate was concentrated to a crystalline residue of **4** (17.2 g, 59%). Mp 150 °C. ^{1}H-NMR ($CDCl_3$): δ 7.4-7.5 (m, 5H), 6.1 (m, 1H), 5.85 (m, 1H), 4.6 (ddd, 1H, J = 8.3, 6.2 and 3.3 Hz), 4.25 (m, 1H), 4.15 (m, 1H), 3.95 (dd, 1H, J = 12.4 and 3.3 Hz), 3.9 (dd, 1H, J = 12.4 and 6.2 Hz).

Example 2

(6R,7R,8S/6S,7S,8R)-2,4-dioxo-7,8-epoxy-6-hydroxymethyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclononane (5). Alcohol **4** (1.00 g, 3.86 mmol) was dissolved in MeCN (30 ml) and water (20 ml) in a flask with an addition funnel, and a dry ice/acetone condenser. The solution was cooled to 0°C with an ice bath, and 1,1,1-trifluoroacetone (4 ml) and $NaHCO_3$ (2.6 g) followed by oxone (12.3 g) was added in small portions over 5 min. The mixture was stirred at room temperature for 18 hours. More $NaHCO_3$ (1.3 g) and oxone (6.15 g) was added, and after 2 hours the reaction was stopped by addition of water (200 ml) followed by extraction with $CHCl_3$ (8 x 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated to a solid mixture of trans and cis epoxides (1.09 g) in ratio 3:1. By addition of $CHCl_3$ (40 ml) the pure transepoxide **5** crystallised (635 mg, 60%). Mp 182-4°C. ^{13}C-NMR ($CDCl_3$): δ 128.3, 127.5, 124.6, 61.1, 54.2, 50.2, 47.6, 41.0.

Example 3

(6R,7R,8R/6S,7S,8S)-7,8-dihydroxy-2,4-dioxo-6-hydroxymethyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclononane (6). Epoxide **5** (500 mg) was dissolved under heating in water (50 ml) and 70% $HClO_4$ (1.25 ml) was added. The solution was heated to 100°C in 5 hours, and then neutralised with potassium carbonate. The solution was concentrated, and the residue was flash-chromatographed in ethyl acetate. Thereby the triol **6** was obtained (388 mg, 73%). ^{13}C-NMR (D_2O): δ 136.6, 133.8, 66.5, 66.2, 61.2, 58.5, 46.1.

Example 4

(4R,5R,6R/4S,5S,6S)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine (1). Triol **6** (256 mg) was dissolved in hydrazine hydrate (5 ml) and heated to 100°C for 18 hours. After evaporation, the residue was flash-chromatographed in EtOH-25% NH_4OH 10:1, giving the title compound **1** (109 mg, 84%) as a syrup. ^{13}C-NMR (D_2O): δ 73.2, 72.7, 64.3, 60.9, 53.0.

Example 5

(*6R/6S*)-2,4-dioxo-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclonon-7-ene-6-carboxylic acid (7). 4-Phenylurazole (**3**, 1.1 g) was dissolved in EtOAc (3 ml) at 0°C, and *tert*-butylhypochlorite (0.7 g) was added, where after a red, homogenous solution was obtained. After 5 min. was added penta-2,4-dienoic acid (0.7 g), and the solution was stirred while being heated over 30 minutes to room temperature. After filtration, the filtrand was washed with pentane (15 ml). Yield of **7**: 1.33 g (79%). ^{1}H-NMR (CD_3OD): δ 7.25 (m, 5H, Ph), 5.95 (s, 2H, H-7 & H-8), 4.95 (bs, 1H, H-6),.4.15 (bd, 1H, *J* 16.7 Hz, H-9a), 3.85 (bd, 1H, *J* 16.7 Hz, H-9b).

Example 6

(*6R/6S*)-2,4-dioxo-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclonon-7-ene-6-carboxylic acid methylester (8). 4-Phenylurazole (**3**, 2.2 g) was dissolved in EtOAc (6 ml) at 0°C, and *tert*-butylhypochlorite (1.1 g) was added where after a red, homogeneous solution was obtained. After 5 min. was added penta-1,3-dienenoic acid methylester (1.5 g), and the solution was stirred while being heated over 30 minutes to room temperature. After filtration, the filtrand was recrystallised from chloroform. Yield of **8**: 3.45 g (97%).^{1}H-NMR ($CDCl_3$): δ 7.4-7.5 (m, 5H, Ph), 6.1 (s, 2H, H-7 & H-8), 5.1 (bs, 1H, H-6),.4.4 (bd, 1H, *J* 16.6 Hz, H-9a), 4.0 (bd, 1H, *J* 16.6 Hz, H-9b), 3.8 (s, 3H, Me).

Example 7

(*6R/6S*)-2,4-dioxo-6-acetoxymethyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclonon-7-ene (9). The alcohol **4** (518 mg) was dissolved in CH_2Cl_2 (10 ml), pyridine (1 ml) and acetic anhydride (1 ml) was added, and the solution was kept at 25°C for 18 hours. The solution was washed with water, HCl and $NaHCO_3$-solutions and dried with $MgSO_4$. After filtration, the filtrate was concentrated to a crystalline residue of **9** (563 mg, 94%). Mp 118-124°C. ^{13}C-NMR ($CDCl_3$): δ 125-8 (3s, Ph), 123.1 (C-8), 121.5 (C-7), 61.8 (C-6'), 52.6 (C-6), 43.7 (C-9), 20.6 (Ac).

Example 8

(*6R/6S*)-2,4-dioxo-6-(2,2,2-trimethylacetoxy)methyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclonon-7-ene (10). Alcohol **4** (1.04 g) was dissolved in CH_2Cl_2 (20 ml), pyridine (2 ml), 4-dimethyl-aminopyridine (10 mg) and pivaloyl chloride (0.97 g) was added, and the solution was kept at 25°C for 3 days. The solution was washed with water, HCl and $NaHCO_3$-solution and was

dried with $MgSO_4$. After filtration, the filtrate was concentrated to a residue of **10** which crystallised from ether (1.11 g, 81%). Mp 97-8°C.

Example 9

(6R,7S,8R/6S,7R,8S)-2,4-dioxo-7,8-epoxy-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclononan-6-carboxylic acid methylester (**11**). Ester **8** (112 mg) was dissolved in CH_2Cl_2 (1 ml), and a solution of dimethyldioxirane in acetone (0.092 M, 18.5 ml, 1.7 mmol, prepared as described by McMurry et al. *J. Org. Chem.* **1985** *50* 2847-53.), was added. The solution was kept at 25°C for 3 days and then concentrated to a solid mixture of trans and cis epoxides (113 mg) in ratio 3:1. Flash-chromatography in EtOAc/pentane 1:1 gave the pure trans epoxide **11** (78 mg, 66%). ^{13}C-NMR ($CDCl_3$): δ 166.7 (C=O), 129.9, 129.1, 126.4 (Ph), 55.4 (C-7), 53.9 (C-8), 50.8 (C-6), 49.5 (OMe), 43.6 (C-9).

Example 10

(6R,7R,8S/6S,7S,8R)-6-acetoxymethyl-2,4-dioxo-7,8-epoxy-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclononane (**12**). Acetate **9** (100 mg) was dissolved in $(CH_2Cl)_2$ (3 ml), and m-chloro-perbenzoic acid (168 mg) was added. The solution was kept at 80°C for 3 hours and cooled. After filtration, the filtrand was washed with CH_2Cl_2 (10 ml), and the filtrates was washed with Na_2CO_3-solution, was dried with $MgSO_4$, filtered and concentrated to a solid mixture (102 mg, 96%) of **12** and the cis epoxide in ratio 2:1. ^{13}C-NMR ($CDCl_3$): δ 130.0, 129.1, 126.3 (Ph), 61.9 (C-6'), 52.5 (C-7), 50.7 (C-8), 48.5 (C-6), 42.7 (C-9), 21.4 (Ac).

Example 11

(6R,7R,8S/6S,7S,8R)-2,4-dioxo-7,8-epoxy-3-phenyl-6-(2,2,2-trimethylacetoxy)methyl-1,3,5-triaza-[4,3,0]-bicyclononane (**13**). Pivalate **10** (79 mg) was dissolved in $(CH_2Cl)_2$ (3 ml), and m-chlorperbenzoic acid (200 mg) was added. The solution was kept at 80°C for 18 hours, and was then cooled. After filtration, the filter was washed with CH_2Cl_2 (10 ml), and the filtrates was washed with Na_2CO_3-solution, was dried with $MgSO_4$, filtered and concentrated to a residue (98 mg). This was purified by flash-chromatography in EtOAc to a syrup (35 mg, 42%) of **13** and the cis epoxide in ratio 3:2. ^{1}H-NMR ($CDCl_3$): δ 7.4-5 (m, 5H, Ph), 4.78 (m, 1H, H-6), 4.69 (dd, 1H, *J* 12.2 & 4.3 Hz, H-6a),. 4.34 (dd, 1H, *J* 12.2 & 3.8 Hz, H-6b),.4.12

(d, 1H, *J* 14.1 Hz, H-9a), 3.99 (dd, 1H, *J* 14.1 & 3.8 Hz, H-9b), 3.59 (m, 1H, H-7), 3.5 (m, 1H, H-8), 1.25 (s, 9H, Me's).

Example 12

(6R/6S)-2,4-dioxo-6-methyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclonon-7-ene (14). 4-Phenylurazole (3, 1.77 g) was dissolved in EtOAc (5 ml) at 0°C, and *tert*-butylhypochlorite (1.1 g) was added, where after a red, homogeneous solution was obtained. After 5 min. was added penta-1,3-diene (1.5 g), and the solution was stirred while being heated over 30 minutes to room temperature. After filtration, the filtrand was washed with chloroform (10 ml), and the filtrates was concentrated to a crystalline residue of **14** (2.22 g, 91%). Mp 122-5 °C. ^{13}C-NMR ($CDCl_3$): δ 129.6, 128.6, 127.9, 125.9, 120.0 (Ph, CH=CH), 50.8 (C-6), 44.0 (C-9), 18.0 (Me).

Example 13

(6R,7R,8S/6S,7S,8R)-7,8-dihydroxy-2,4-dioxo-6-methyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclononane (15). Alkene **14** (564 mg) was dissolved in water (1 ml) and acetone (1 ml), and N-methylmorpholin-N-oxide (400 mg) was added. Finally was added 1 ml of a solution of OsO_4 in butanol (10 g/l), and the solution was kept at 25°C for 4 days. A solution of 0.5 g $Na_2S_2O_5$ in 30 ml water was added, and extraction with ethyl acetate (5x 20 ml) was performed. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. From the residue was crystallised diol **15** (431 mg, 67%) with EtOAc-ether. ^{13}C-NMR (CD_3CN/D_2O): δ 128.3, 127.5, 125.8 (Ph), 69.3 (C-7), 63.0 (C-8), 54.3 (C-6), 43.2 (C-9), 17.8 (C-6').

Example 14

(4R,5S,6S/4S,5R,6R)-4,5-dihydroxy-6-methyl-hexahydropyridazine (16). Diol **15** (176 mg) was dissolved in hydrazinhydrate (10 ml) and warmed to 100 °C for 18 hours. Then it was concentrated, and the residue was flash-chromatographed in EtOH-25% NH_4OH 50:1, where after the compound **16** (76 mg, 90%) was obtained as a syrup. ^{13}C-NMR (D_2O): δ 75.7 (C-5), 69.0 (C-4), 55.2 (C-6), 54.3 (C-3), 17.8 (C-6').

Example 15

(6R,7R,8S/6S,7S,8R)-7,8-dihydroxy-2,4-dioxo-6-hydroxymethyl-3-phenyl-1,3,5-triaza-[4,3,0]-bicyclononane (17). Alkene **4** (601 mg) was dissolved in water (1 ml) and acetone (1 ml), and N-methylmorpholine-N-oxide (400 mg) was added. Finally was added 1 ml of a solution of OsO_4 in butanol (10 g/l), and the solution was kept at 25°C for 5 days. 0.5 g of $Na_2S_2O_5$ was added, and the mixture was concentrated. The residue was soxlet-extracted with acetone (100 ml). The organic layers were concentrated. From the residue crystallised from acetone the triol **17** (537 mg, 79%). ^{13}C-NMR (CD_3CN/D_2O): δ 151.3, 150.6 (C=O), 128.6, 127.6, 127.3, 124.8 (Ph), 63.6 (C-7), 61.9 (C-8), 58.2 (C-6'), 56.3 (C-6), 42.5 (C-9).

Example 16

(4R,5S,6S/4S,5R,6R)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine (18). Triol **17** (180 mg) was dissolved in hydrazinhydrate (10 ml) and warmed to 100 °C for 24 hours. Then the solution was concentrated, and the residue was flash-chromatographed in EtOH-25% NH_4OH 20:1, giving the compound **18** as a syrup (85 mg, 93%). ^{13}C-NMR (D_2O): δ 70.4 (C-5), 68.9 (C-4), 63.0 (C-6'), 60.7 (C-6), 54.1 (C-3).

Example 17

Enzyme assays: Enzymes and substrates were obtained from Sigma. As substrate was employed p-nitrophenyl-α-glucopyranoside for α-glucosidase and p-nitrophenyl-β-glucopyranoside for β-glucosidase. The experiments were performed in 0.05 M phosphate buffer at 22°C. Enzyme assays were performed as described by H. Halvorson *Methods Enzym.* 8 (1966) 559-62.

Enzyme	α-glucosidase	β-glucosidase
Ki (μM, pH= 7.5)		1.02
Ki (μM, pH= 6.8)	3.72	0.61
Ki (μM, pH= 5.0)		0.72

Table 1. Inhibitor constants for **1**.

Example 18

Glycogen phosphorylase inhibition: The assay which was described by Johnson et al. (*Biochemistry* **1991** *30* 10101-16.) was used. Glycogen phosphorylase A was bought from Sigma. As substrate was used α-D-glucopyranose 1-phosphate (0.1 M) and a 4% glycogen-solution. The experiments were performed in 0.1 M NaF/HCl buffer, pH 6.2 at temperature 26°C. The reaction was followed in direction of glycogen synthesis, as phosphate development was measured as described by Palmgren et al. *The Plant Cell* **1995** *7* 1655-6.

[compound] μM	% inhibition
3.7	16
37	66
3700	78

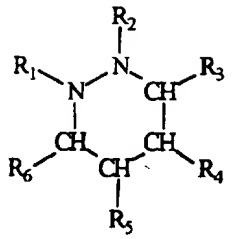
Table 2. Inhibition constants for **1**.

The results in table 2 can be extrapolated to a IC_{50} value of 13.5 μM.

The chemical compound **1** and related compounds are strong inhibitors of glycoside-cleaving enzymes. This is illustrated in table 1 where it can be seen that **1** show potent inhibition of α-glucosidase from bakers yeast and β-glucosidase from almonds.

CLAIMS

1. A compound of the general formula I



wherein

R_1 designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, optionally substituted C_{1-7}-alkylcarbonyl, optionally substituted C_{1-7}-alkoxycarbonyl, optionally substituted aryl(C_{1-7}-alkoxy)carbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy or $-CH_2-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; or R_1 designates two C_{1-7}-alkyl groups thereby leading to a quaternarisation of the nitrogen atom to which R_1 (the two C_{1-7}-alkyl groups) is/are attached; and

R_2 designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy or $-CH_2-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide;

each of R_3, R_4, R_5, and R_6 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, amino, optionally substituted C_{1-7}-alkylamino, di(optionally substituted C_{1-7}-alkyl)amino, tri(optionally substituted C_{1-7}-alkyl)ammonium, carboxy, carboxyamino, optionally substituted C_{1-7}-alkylcarbonylamino, optionally substituted arylcarbonylamino, nitro, sulphanyl, C_{1-7}-alkylthio, cyano, azido, optionally substituted C_{2-7}-alkenyl, optionally substituted C_{2-7}-alkynyl, optionally substituted aryl, optionally substituted C_{1-7}-alkylcarbonyl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted

C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or -CH_2-O-X or -O-X, where X designates a glycosyl group of a mono-, di- or trisaccharide;

or a salt thereof;

with the provisos that

(a) at least one of R_3, R_4, R_5 or R_6 designates optionally substituted C_{1-7}-alkyl, carboxy, cyano, optionally substituted C_{2-7}-alkenyl, optionally substituted C_{2-7}-alkynyl, optionally substituted aryl, optionally substituted C_{1-7}-alkylcarbonyl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, or -CH_2-O-X, where X designates a glycosyl group of a mono-, di- or trisaccharide; and

(b) at least one of R_3, R_4, R_5 or R_6 designates hydroxy, optionally substituted C_{1-7}-alkoxy, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or -O-X, where X designates a glycosyl group of a mono-, di- or trisaccharide; and

(c) when R_3 designate (3S)-carboxy and R_4 and R_6 designate hydrogen, then R_5 designates a group different from (5S)-hydroxy; and

(d) that said compound is not selected from 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-hydroxy-1,2-diazinane, 1-*tert*-butoxycarbonyl-3-ethoxycarbonyl-4-acetoxy-1,2-diazinane, (3R, 4S, 5R, 6S)-6-methyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4S, 5R, 6S)-6-methyl-3,4,5-trihydroxy-1,2-diazinane, (3R, 4S, 5R, 6S)-1,6-dimethyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4S, 5R, 6S)-1,6-dimethyl-3,4,5-trihydroxy-1,2-diazinane, (3S, 4R, 5R)-3-methyl-4,5-dihydroxy-1,2-diazinane, (3S, 4R, 5R)-1-acetyl-3-methyl-4,5-dihydroxy-1,2-diazinane, (3S, 4R, 5R)-1-acetyl-4,5-diacetoxy-3-methyl-1,2-diazinane.

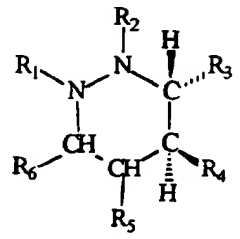
2. A compound according to claim 1, wherein R_1 designates hydrogen, optionally substituted C_{1-7}-alkyl, optionally substituted C_{1-7}-alkylcarbonyl, aryl(C_{1-7}-alkoxy)carbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)amino-carbonyl, or optionally substituted C_{1-7}-alkylcarbonyloxy; or R_1 designates two C_{1-7}-alkyl groups; and R_2 designates hydrogen or optionally substituted C_{1-7}-alkyl; and each of R_3, R_4, R_5, and R_6 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, amino, optionally substituted C_{1-7}-alkylamino, di(optionally substituted C_{1-7}-alkyl)amino,

tri(optionally substituted C_{1-7}-alkyl)ammonium, carboxy, carboxyamino, optionally substituted C_{1-7}-alkylcarbonylamino, optionally substituted arylcarbonylamino, sulphanyl, C_{1-7}-alkylthio, cyano, azido, optionally substituted aryl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; or a salt thereof.

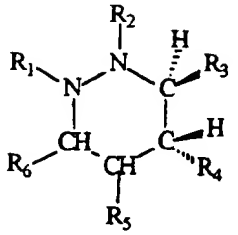
3. A compound according to claim 1 or 2, wherein each of R_1 and R_2 independently designates hydrogen or optionally substituted C_{1-7}-alkyl; and each of R_3 and R_6 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, carboxy, cyano, azido, optionally substituted aryl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; each of R_4 and R_5 independently designates hydrogen, hydroxy, halogen, optionally substituted C_{1-7}-alkyl, amino, optionally substituted C_{1-7}-alkylamino, di(optionally substituted C_{1-7}-alkyl)amino, carboxy, carboxyamino, optionally substituted C_{1-7}-alkylcarbonylamino, optionally substituted arylcarbonylamino, sulphanyl, C_{1-7}-alkylthio, cyano, azido, optionally substituted aryl, optionally substituted C_{1-7}-alkoxycarbonyl, aminocarbonyl, optionally substituted C_{1-7}-alkylaminocarbonyl, di(optionally substituted C_{1-7}-alkyl)aminocarbonyl, optionally substituted C_{2-7}-alkenyloxy, optionally substituted C_{1-7}-alkylcarbonyloxy, or $-CH_2-O-X$ or $-O-X$, where X designates a glycosyl group of a mono-, di- or trisaccharide; or a salt thereof.

4. A compound according to any of the claims 1-3, wherein each of R_1 and R_2 independently designates hydrogen or C_{1-7}-alkyl; and each of R_3 and R_6 independently designates hydrogen, hydroxy, C_{1-7}-alkyl, carboxy, cyano, azido, C_{1-7}-alkoxycarbonyl, aminocarbonyl, C_{1-7}-alkylaminocarbonyl, or di(C_{1-7}-alkyl)aminocarbonyl; each of R_4 and R_5 independently designates hydrogen, hydroxy, C_{1-7}-alkyl, amino, C_{1-7}-alkylamino, di(C_{1-7}-alkyl)amino, carboxy, carboxyamino, C_{1-7}-alkylcarbonylamino, cyano, azido, optionally substituted aryl, C_{1-7}-alkoxycarbonyl, aminocarbonyl, C_{1-7}-alkylaminocarbonyl, di(C_{1-7}-alkyl)aminocarbonyl, or C_{1-7}-alkylcarbonyloxy; or a salt thereof.

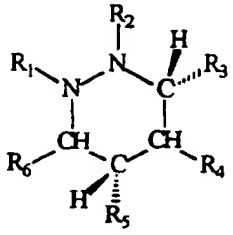
5. A compound according to any of the claims 1-4, which is of any of the general formulae II, III, IV or V



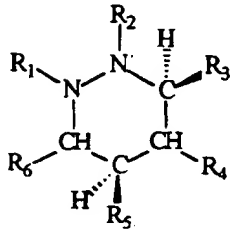
II



III



IV



V

6. A compound according to claim 1 or 5, wherein R_1 designates hydrogen, hydroxy, hydroxy-(C_{1-7}-alkyl), halogen, C_{1-7}-alkyl, C_{1-7}-alkanoyl, C_{1-7}-alkanoyloxy or C_{1-7}-alkoxy, or R_1 may designate two C_{1-7}-alkyl groups thereby leading to a quaternarisation of the nitrogen to which R_1 (the two alkyl groups) is/are attached; R_2 designates hydrogen, hydroxy, hydroxy-(C_{1-7}-alkyl), halogen, C_{1-7}-alkyl, C_{1-7}-alkanoyloxy, or C_{1-7}-alkoxy; each of R_3, R_4, R_5, and R_6 independently designates hydrogen, hydroxy, hydroxy-(C_{1-7}-alkyl), amino, C_{1-7}-alkylamino, di(C_{1-7}-alkyl)amino, C_{1-7}-alkanoylamino, tri(C_{1-7}-alkyl)ammonium, halogen, nitro, sulphanyl, C_{1-7}-alkylthio, carboxy, cyano, C_{2-7}-alkenyl, phenyl, C_{1-7}-alkylphenyl, C_{1-7}-alkyl, C_{1-7}-alkanoyl, C_{1-7}-alkanoyloxy or C_{1-7}-alkoxy; with the proviso that at least one of R_3, R_4, R_5 and R_6 designate(s) hydroxy, C_{1-7}-alkanoyloxy, or C_{1-7}-alkoxy; and at least one of R_3, R_4, R_5 and R_6 designate(s) hydroxy-(C_{1-7}-alkyl), carboxy, cyano, C_{2-7}-alkenyl, phenyl, C_{1-7}-alkylphenyl, C_{1-7}-alkyl or C_{1-7}-alkanoyl; or a salt thereof, wherein (a) any alkyl is optionally substituted with one or more, preferably 1-3, substituents selected from hydroxy, C_{1-7}-alkoxy, carboxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-7}-alkyl)amino, carbamoyl, mono- and di(C_{1-7}-alkyl)aminocarbonyl, guanidino, carbamido, C_{1-7}-alkanoyloxy, sulphono, nitro, C_{1-7}-alkylthio, trihalogenalkyl and halogen; (b) any alkanoyl group is optionally substituted 1 or more, preferably 1-3, substituents selected from hydroxy, C_{1-7}-alkoxy,

carboxy, C_{1-7}-alkoxycarbonyl, C_{1-7}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-7}-alkyl)amino, carbamoyl, mono- and di(C_{1-7}-alkyl)aminocarbonyl, guanidino, carbamido, C_{1-7}-alkanoyloxy, sulphono, nitro, C_{1-7}-alkylthio, trihalogenalkyl and halogen; and (c) any phenyl group is optionally substituted with 1-3 substituents selected from halogen, methoxy, trifluoromethyl, and methyl.

7. A compound according to any of the claims 1-6, which is one of
4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine
4,5-dihydroxy-6-methyl-hexahydropyridazine,
4,5-dihydroxy-6-fluoromethyl-hexahydropyridazine,
4-fluoro-5-hydroxy-6-hydroxymethyl-hexahydropyridazine,
1-N-(2-hydroxyethyl)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,
2-N-(2-hydroxyethyl)-4,5-dihydroxy-6-hydroxymethyl-hexahydropyridazine,
4,5-dihydroxy-hexahydropyridazine-6-carboxylic acid;
and salt thereof.

8. A compound according to any of the claims 1-7 for use as a medicament.

9. A compound according to any of the claims 1-7 for treatment of or for controlling diabetes.

10. A compound according to any of the claims 1-7 for treatment of or for controlling cancer.

11. A compound according to any of the claims 1-7 for fighting or controlling human immunodeficiency virus.

12. The use of a compound according to any of the claims 1-7 for protecting an agricultural crop.

13. The use of a compound according to any of the claims 1-7 for inhibiting cellulase activity.

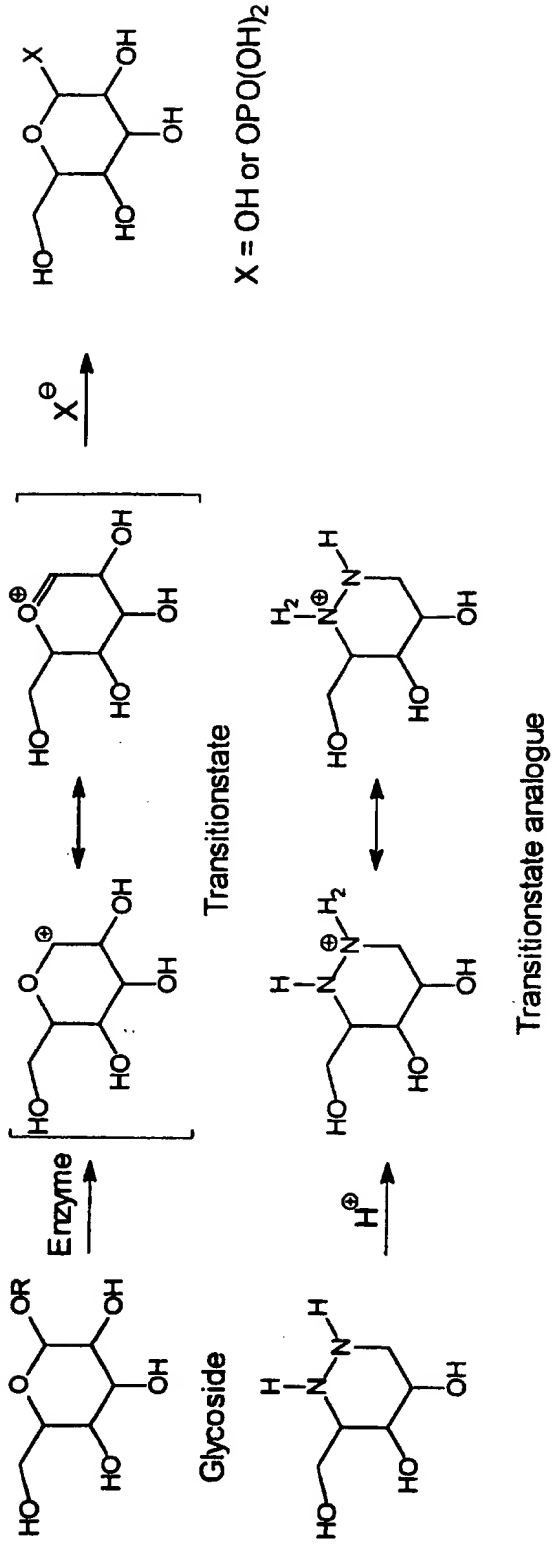

X = OH or OPO(OH)2
X⊖
Transitionstate
Enzyme
Glycoside
H⊕
Transitionstate analogue

Figure 1

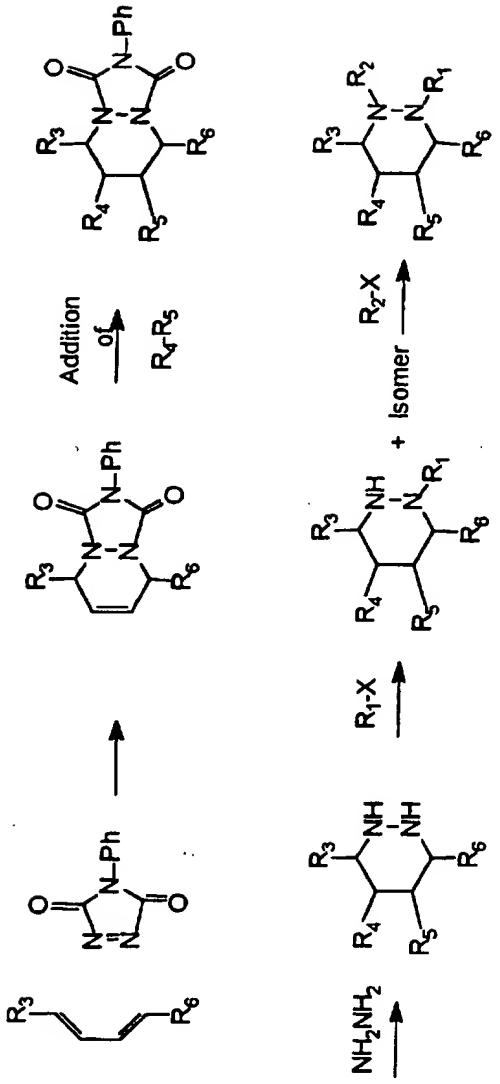


Figure 2

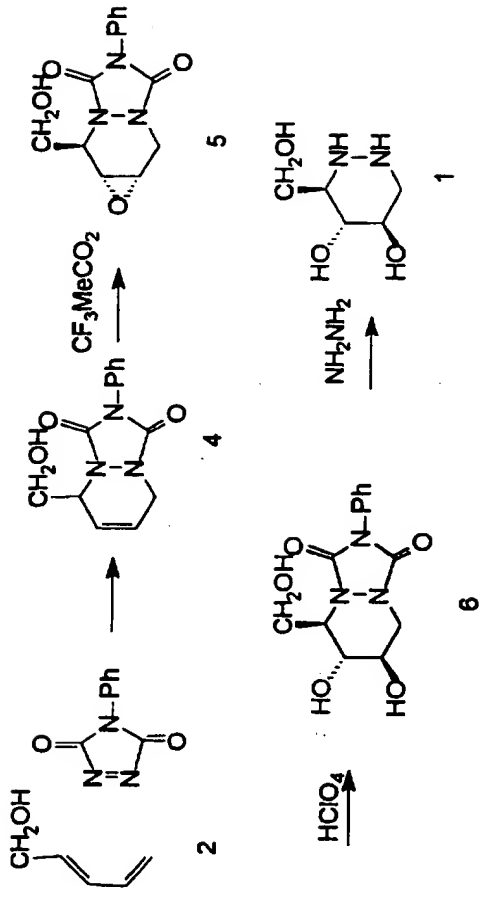


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00090

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 237/04, A61K 31/495, A01N 43/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0621270 A1 (SANKYO COMPANY LIMITED), 26 October 1994 (26.10.94) --	1-8,10
A	J. CHEM. SOC., CHEM. COMMUN, Marco A. Ciufolini et al: "Synthesis and Chemical Properties of PCA, an Unusual Amino Acid in Luzopeptins", 1994, page 1867 - page 1868 --	1-12
A	Chem. Ber., Volume 103, 1970, Hans Paulsen et al, "Cyclisierung von 4.5-Didesoxy-4-hydrazino-L-xylose zu einem Sechsring-Hydrazon" page 1834 - page 1845 --	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 1997	25.06.97
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00090

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3105833 A (RUDOLF GABLER ET AL), 1 October 1963 (01.10.63) -- --------	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00090

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/06/97

International application No.
PCT/DK 97/00090

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0621270 A1	26/10/94	AU 661058 B	13/07/95
		FI 942094 A	01/07/94
		NO 941698 A	07/07/94
		AU 2799392 A	07/06/93
		CA 2123104 A	13/05/93
		CZ 9401126 A	15/12/94
		HU 67374 A	28/03/95
		HU 9401420 D	00/00/00
		JP 5194414 A	03/08/93
		JP 5194415 A	03/08/93
		WO 9309097 A	13/05/93
US 3105833 A	01/10/63	NONE	